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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,037	01/19/2005	Klaus Michael Debatin	085449-0152	6277
22428	7590	03/17/2009	EXAMINER	
FOLEY AND LARDNER LLP			SANG, HONG	
SUITE 500				
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WASHINGTON, DC 20007			PAPER NUMBER	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b>	<b>Application No.</b> 10/511,037	<b>Applicant(s)</b> DEBATIN ET AL.	
	<b>Examiner</b> HONG SANG	<b>Art Unit</b> 1643	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 18 February 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.  
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b) ☐ They raise the issue of new matter (see NOTE below);  
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
 5. ☒ Applicant's reply has overcome the following rejection(s): NONE.  
 6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
 7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
 The status of the claim(s) is (or will be) as follows:  
 Claim(s) allowed: \_\_\_\_\_.  
 Claim(s) objected to: \_\_\_\_\_.  
 Claim(s) rejected: 45-52.  
 Claim(s) withdrawn from consideration: 35-43.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see continuation sheet.  
 12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_  
 13. ☐ Other: \_\_\_\_\_.

/Christopher H Yaen/  
 Primary Examiner, Art Unit 1643

Continuation of 11. does NOT place the application in condition for allowance because applicant's arguments are not persuasive to overcome the rejections of record. Specifically, applicants argue that Ford reference teaches away from the instant invention and the examiner is relying upon impermissible hindsight. Applicant's arguments have been carefully considered but are not persuasive. Ford et al. disclose that many proteins have been successfully transported into a wide variety of human and murine cell types using the TAT PTD methodology (see page 2, column 2, paragraph 2). The molecules which have been successfully transported into cells in vitro and in vivo include large proteins and small peptides (see page 2, column 2). Ford et al. disclose that denatured TAT protein as well as regions of the TAT protein have shown to be able to efficiently transport proteins and peptides into cells (see page 2, column 2). Ford et al. expressly state that protein transduction may also enable more efficient penetration and delivery at solid tumor sites (see page 3, column 1, last paragraph). While the full length TAT protein has been shown to stimulate growth of Kaposi's sarcoma-derived cells, the claims are not drawn to a method of treating sarcoma. There is no teaching in the art that TAT protein stimulates growth of any other cancer cells. The instant claims encompass using regions of the TAT protein, which are not known to be tumorigenic. Furthermore, the instant claims are drawn to a product per se (emphasis added). The motivation to make a TAT-SMAC fusion protein may simply be in vitro delivery of SMAC into different cells including tumor cells and further study of the functions and apoptotic effects of SMAC proteins in different cells. One of skilled in the art would have had a reasonable expectation to make a fusion protein comprising TAT-SMAC because methods of making fusion proteins were well known in the art at the time the instant invention was made. In response to arguments that Ford et al. do not specifically teach using TAT PAD to transport chemotherapeutic agents into cancer cells, Applicants are reminded the instant rejection is 103(a) rejection. Ford et al. disclose using PTD methodology to transport chemotherapeutic agents. It would have been obvious to one skilled in the art to use any of the three disclosed PAD molecules to transport chemotherapeutic agents. Finally, applicant argued that the examiner uses hindsight reasoning to establish the prima facie case. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. "Any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *Ln re McLaughlin* 443. F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). In the instant case, the prior art teach SMAC proteins can induce cancer cell apoptosis and TAT has been used successfully to transported peptides and proteins into various types of cells. Thus the use of TAT or fragments thereof to transport SMAC proteins into different cells including tumor cells to study the function and effect of SMAC proteins in the cells, was clearly in the purview of those of ordinary skill in the art and was within the knowledge of 'those in the art at the time the invention was made. Because of these reasons, the rejection is deemed proper and therefore maintained.

The objection to claim 46 is withdrawn in view of applicant's amendment to the claim.

The notice to comply with sequence rules is withdrawn in view of applicant's arguments.